



# A systematic review of active treatment options in patients with desmoid tumours

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## ABSTRACT

### Introduction

We conducted a systematic review to determine the optimal treatment options in patients with desmoid tumours who have declined observational management.

### Methods

A search was conducted of the MEDLINE and EMBASE databases (1990 to September 2012), the Cochrane Library, and relevant guideline Web sites and conference materials.

### Results

One systematic review and forty-six studies met the preplanned study selection criteria; data from twenty-eight articles were extracted and analyzed. For local control, three studies reported a statistically significant difference in favour of surgery plus radiotherapy (RT) compared with surgery alone, and one study did not; two studies reported the lack of a statistical difference between surgery plus RT and RT alone in maintaining local control. Multivariate risk factors for local recurrence included positive surgical margins and young patient age. Single-agent imatinib led to a progression-free survival rate of 55% at 2 years and 58% at 3 years. Methotrexate plus vinblastine led to a progression-free survival rate of 67% at 10 years. Significant toxicities were reported for all treatment modalities, including surgical morbidity, and RT- and chemotherapy-related toxicities.

### Conclusions

In patients who have declined observational management, the local control rate was higher with surgery plus RT than with surgery alone. However, the additional RT-related complications should be

considered in treatment decision-making. Surgery, RT, and systemic therapy are all reasonable treatment options for patients with desmoid tumours.

## KEY WORDS

Desmoid tumours, systematic review, treatments

## 1. INTRODUCTION

Desmoid tumours, also known as aggressive fibromatoses, are rare neoplasms arising from fascial or deep musculoaponeurotic structures. They are localized in the abdominal wall, the bowel, the mesentery (associated with familial adenomatous polyposis), and extra-abdominal sites<sup>1</sup>. The incidence of desmoid tumours is 2–4 new cases per million inhabitants per year<sup>1,2</sup>.

Desmoid tumours are non-malignant and non-metastasizing, and they seldom cause death; however, they are locally invasive, they easily recur, and they cause significant morbidity because of pain<sup>2</sup>. They may be asymptomatic, but they most often cause local or neuropathic pain (or both), compress local structures, and inhibit function, and they can be cosmetically unappealing. They have a variable course, with some growing to a large size and others remaining stable without intervention. Clinical observation is therefore a viable option in asymptomatic patients.

For patients with desmoid tumours for whom the decision has been made to pursue active (non-observational) therapy, several treatments are available, including surgery, radiotherapy (RT), systemic therapy, and combinations of those options. However, there is little consensus about which strategy or combination of strategies results in a lower recurrence rate and less toxicity, and thus represents the ideal approach. The Sarcoma Disease Site Group, in association with the Program in Evidence-Based Care of Cancer Care Ontario, therefore conducted a systematic review to determine the optimal treatment

options in patients with desmoid tumours who have declined observational management.

## 2. METHODS

### 2.1 Search for Existing Systematic Reviews and Guidelines

The following resources were searched for existing systematic reviews and practice guidelines: the Cochrane Library (to Issue 12, 2012); the National Guideline Clearinghouse (United States), the National Health and Medical Research Council (Australia), the New Zealand Guidelines Group, the American Society of Clinical Oncology, the National Institute for Health and Clinical Excellence (United Kingdom), the Scottish Intercollegiate Guidelines Network, the Society of Obstetricians and Gynaecologists of Canada, and the Gynecologic Oncology Group (to September 19, 2012); and the Standards and Guidelines Evidence directory maintained by the Canadian Partnership Against Cancer (to August 12, 2012)<sup>3</sup>.

### 2.2 Primary Literature Systematic Review

If no existing systematic reviews or practice guidelines based on a systematic review were identified, the Cochrane Central Register of Controlled Trials (to October 2012) and the MEDLINE and EMBASE databases (from January 1, 1990, to September 28, 2012) were searched to find full publications. The American Society of Clinical Oncology annual meeting abstracts and the Connective Tissue Oncology Society annual meeting abstracts from January 2009 to September 2012 were also searched for abstracts that met the study selection criteria outlined in the next subsection. The search strategies are reported in Table 1.

#### 2.2.1 Study Selection Criteria

An article was eligible for inclusion if it met all the following preplanned criteria:

- It was a full-text report published in the period from January 1, 1990, to September 28, 2012, or a conference or meeting abstract published from January 2009 to October 2012.
- If a full-text report, it reported either a systematic review (defined as describing search databases, search time period, search terms, and study selection criteria; and having at least one eligible article that met our study selection criteria for original studies), a randomized controlled trial (RCT), a comparative study with an analyzed sample size of 30 patients or more, or prospective single-arm study with an analyzed sample size of 30 patients or more.
- If a conference or meeting abstract, it reported a RCT.

TABLE 1 MEDLINE and EMBASE search strategies

1	exp fibromatosis/ or fibromatos\$.mp.
2	desmoid tumo?r\$.mp.
3	1 or 2
4	(treatment\$ or therap\$).mp.
5	(surger\$ or radiotherap\$ or chemotherap\$ or radiation\$ or therapeutic\$ or immunotherap\$).mp.
6	anti-inflammatory.mp. or exp Anti-Inflammatory Agents/
7	(hormon\$ or cytotoxic\$).mp.
8	(methotrexat\$ or vinorelbine or vinblastine or imatinib or sorafenib or doxorubicin or tamoxifen or sulindac).mp.
9	Antineoplastic Agents/
10	or/4–9
11	(comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
12	(3 and 10) not 11
13	limit 12 to (english language and yr="1990 -Current")

- It investigated surgery, RT, systemic therapy, or any combination thereof in patients with desmoid tumours.
- It reported at least one of the following clinical outcomes: relapse-free or progression-free survival, local control rate, response rate, toxicity, and patient-reported outcomes.

Articles or abstracts were excluded if they met any of the following preplanned criteria:

- They were published in a language other than English.
- They were published in the form of a letter, animal study, editorial, or commentary.

The titles and abstracts that resulted from the search were reviewed by one reviewer (XY). For items that warranted full-text review, XY reviewed each one and discussed with the other working group members (MG, TC, AAG, RAK, SV, JW) to confirm the final study selections. All extracted data were audited by a second, independent auditor (Caitlin Ireland).

#### 2.2.2 Synthesizing the Evidence

For the comparative non-RCT studies that met the preplanned study selection criteria, we identified studies that did not use multivariate analysis to control for differences in baseline patient characteristics. The studies thus identified were summarized in tables for toxicity analysis, but were not included in the interpretive synthesis of intervention effectiveness because of the potential likelihood

of biased outcomes resulting from confounding variables at baseline.

### 3. RESULTS

#### 3.1 Search for Existing Systematic Reviews or Guidelines

No existing systematic reviews or guidelines that met the preplanned criteria addressing the research question were found.

#### 3.2 Primary Literature Systematic Review

##### 3.2.1 Literature Search Results

Of 3791 citations identified from the searches of the MEDLINE and EMBASE databases and the Cochrane Central Register of Controlled Trials (Figure 1), 3579 articles were excluded after review of the titles and abstracts; another 164 were disqualified after review of the full text. The search of the American Society of Clinical Oncology and Connective Tissue Oncology Society annual meeting abstracts yielded no abstracts that met the study selection criteria. Ultimately, one systematic review<sup>4</sup> and forty-six full text articles<sup>5–50</sup>

were included in the present systematic review. The reference lists of the included articles were hand-searched, and no further eligible papers were found.

The review by Nuyttens *et al.*<sup>4</sup> pooled the data from twenty-two single-arm or comparative studies published from 1983 to 1998, but did not take the clinical heterogeneity of the studies (such as varying tumour size, tumour location, patient age, primary or recurrent presentation, and so on) into account, which was determined to represent weak methodology. That systematic review was therefore not used as the core of the evidentiary base and was not included for further analysis. The studies included in the Nuyttens review either replicated some of the forty-six eligible articles used in this systematic review or did not meet our study selection criteria.

Fifteen articles that did not provide clear comparative data for each group were excluded from further analysis<sup>33–47</sup>.

Several articles that represented multiple reports for the same study population warrant further comment. The patients in the 1990 Sherman *et al.* study<sup>48</sup> and the 1998 Ballo *et al.* study<sup>50</sup> were included in the 1999 Ballo *et al.* paper<sup>11</sup>. Most of the patients in the 1995 Faulkner *et al.* paper<sup>49</sup> were reported in the

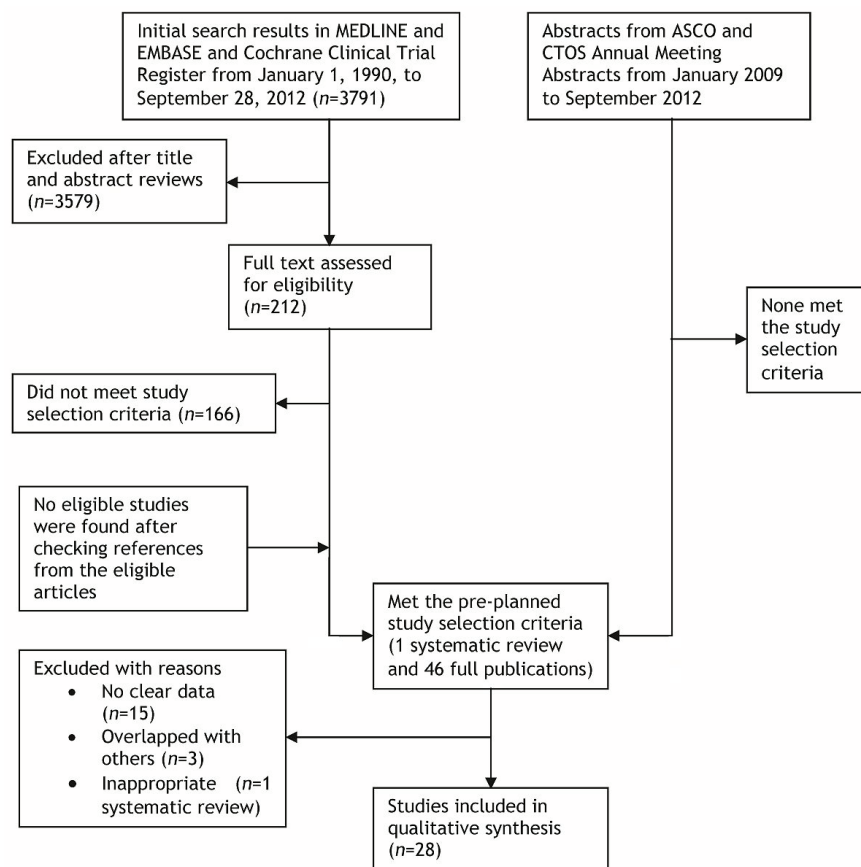


FIGURE 1 Flow diagram of studies considered in this systematic review. ASCO = American Society of Clinical Oncology; CTOS = Connective Tissue Oncology Society.

1992 Brodsky *et al.* article<sup>5</sup> or the 1999 Merchant *et al.* article<sup>12</sup>. As a result, the articles by Sherman *et al.* (1990), Ballo *et al.* (1998), and Faulkner *et al.* (1995) were omitted from the tables and text. Thus, data from twenty-eight articles were abstracted and summarized in this systematic review<sup>5–32</sup>.

### 3.2.2 Study Design and Quality

Four articles reported prospective single-arm studies<sup>15,18,23,28</sup>, one was a historical prospective comparative study<sup>31</sup>, and the other twenty-three were retrospective comparative studies (Table II). Study quality was assessed using the modified Newcastle–Ottawa Scale<sup>51</sup> (detailed table available from the corresponding author). In the twenty-four comparative studies, the patients in the control group were selected from the same hospital in which the study was performed. Four studies included patients with primary desmoid tumours<sup>8,12,17,32</sup>. Only one retrospective study compared the main clinical characteristics of the patients at baseline, showing no significant differences between the intervention groups<sup>25</sup>; however, five studies conducted a multivariate analysis to control for potential confounders at baseline<sup>9–11,17,22</sup>. Only two studies reported a blinded assessment of outcome<sup>23,28</sup>. The follow-up rates in twenty-three studies exceeded 80%. Overall, the study quality from the included studies was poor to moderate.

### 3.2.3 Outcomes

In the twenty-eight included studies, the sample size ranged from 30 to 234. In twenty-two articles, the study had recruited children; patient ages ranged from 0 to 86 years, and the mean or median age ranged from 7 to 41 years. The proportion of female patients ranged from 46% to 79%.

Meta-analyses of the trial results were considered, but were deemed not feasible because the heterogeneity of the patients, tumour sizes, tumour presentations (primary or recurrent), tumour locations, margin status, interventions, intervention doses, toxicity or complication assessment criteria, and tumour response assessment criteria were too great to allow for pooling of data.

**Surgery Versus RT Versus Surgery Plus RT:** Table III shows the clinical outcomes from the twenty-one studies that compared surgery with RT, or surgery with surgery plus RT, or RT with surgery plus RT<sup>5–14,16,17,19–22,24,25,27,29,32</sup>, and the one prospective single-arm study that investigated the effect of surgery plus RT<sup>18</sup>. In those studies, the mean or median age of the patients ranged from 7 to 41 years, with an overall range of 0–83 years (Table II). The radiation doses ranged from 10 Gy to 75 Gy when RT was used alone and from 9 Gy to 72 Gy when RT was used as an adjuvant to surgery. Table IV lists the variables that, in the five comparative studies that conducted multivariate analyses to control for potential confounders<sup>9–11,17,22</sup>, appeared in the

multivariate model and were identified to significantly relate to the local control rate.

**Local Control Rate:** Three of the included studies with a total sample size of 306 patients<sup>9–11</sup> reported a statistically significant higher local control rate in the surgery plus RT group than in the surgery-alone group; one study with 72 patients<sup>17</sup> found no difference between those two groups.

When surgery plus RT was compared with RT alone, the 2008 Guadagnolo *et al.* and 2010 Rüdiger *et al.* studies<sup>22,25</sup>, with a total of 149 patients, reported no statistical difference in local control rates between those two groups at 4 or 10 years.

**Toxicity:** Eight of the articles reported toxicities or complications after surgery or RT (Table III). One study used the U.S. National Cancer Institute *Common Terminology Criteria for Adverse Events* to assess RT toxicity<sup>29</sup>, three studies used their own criteria<sup>9,16,22</sup>, and four studies did not clarify the criteria used to assess toxicities or complications<sup>6,18,21,27</sup>.

Two studies reported complications after surgical treatment. The 1997 Goy *et al.*<sup>9</sup> study found that 2% of patients were disabled, 2% had above-the-knee amputation, and 7% needed reconstructive surgery. The 2011 Gluck *et al.*<sup>27</sup> study reported that 2% of patients had chronic pain.

The main radiation-related complications included mesothelioma, carcinosarcoma, and melanoma with a radiation dose of 44–75 Gy<sup>22</sup>; fibrosarcoma, femur and femoral nail fractures, and wound complications needing surgical management with 50 Gy<sup>18</sup>; secondary gastric cancer, large muscular defect, and nonhealing tissue defect with 50–68 Gy<sup>27</sup>; and lymphedema, radial or ulnar synostosis, basal cell carcinoma, fracture, and cellulitis with 35–65 Gy<sup>29</sup>.

**Patient-Reported Outcomes:** No study described patient-reported outcomes.

**Systemic Therapy:** Among the six eligible studies of systemic therapy (Table V), the mean or median age of the patients ranged from 27 to 41 years, with an overall range of 4–72 years (Table II). In three comparative studies<sup>26,30,31</sup>, patient characteristics either were not compared at baseline or were significantly different between the groups at baseline, and no multivariate analysis for outcomes was conducted. Those studies are summarized in our tables, but are not included in the interpretive synthesis of intervention effectiveness because of the potential likelihood of biased outcomes resulting from confounding variables at baseline.

In three phase II single-arm studies, 75% or more of the patients had recurrent tumours<sup>15,23,28</sup>. Azzarelli *et al.*<sup>15</sup> reported that methotrexate plus vinblastine led to a progression-free survival rate of 67% at 5 and 10 years and a 100% rate of partial response or stable

disease at a median of 1 year during the treatment period in 30 patients; however, 93% of the patients experienced grade 3 or 4 leukopenia. Chugh *et al.*<sup>23</sup> reported a progression-free survival rate of 58% at 3 years and a stable disease rate of 84% at 4 months in 51 patients on imatinib treatment, but 8%–10% of patients experienced grade 3 or 4 neutropenia, rash, or fatigue. Penel *et al.*<sup>28</sup> also found that imatinib

resulted in a progression-free survival rate of 55% at 2 years, but that treatment was associated with grades 3 and 4 toxicity, including rash, abdominal pain, vomiting or nausea, diarrhea, myalgia, asthenia, or clear cell renal carcinoma.

*Patient-Reported Outcomes:* No study described patient-reported outcomes.

TABLE II Study design and patient characteristics

Reference	Country	Design	Patients (n)	Age (years)		Sex (% women)
				Mean or median	Range	
<i>Studies of surgery versus surgery plus RT versus RT alone</i>						
Brodsky <i>et al.</i> , 1992 <sup>5</sup>	U.S.A.	Retrospective comparative	32	36	12–67	59
Acker <i>et al.</i> , 1993 <sup>6,a</sup>	U.S.A.	Retrospective comparative	40	28	0.2–74	63
Catton <i>et al.</i> , 1995 <sup>7</sup>	Canada	Retrospective comparative	40	31	11–78	68
Pritchard <i>et al.</i> , 1996 <sup>8</sup>	U.S.A.	Retrospective comparative	44	40	9–83	62
Goy <i>et al.</i> , 1997 <sup>9</sup>	U.S.A.	Retrospective comparative	56	32	10–64	70
Spear <i>et al.</i> , 1998 <sup>10</sup>	U.S.A.	Retrospective comparative	105	32	NR	65
Ballo <i>et al.</i> , 1999 <sup>11</sup>	U.S.A.	Retrospective comparative	189	31	1–81	57
Merchant <i>et al.</i> , 1999 <sup>12</sup>	U.S.A.	Retrospective comparative	105	35	16–79	74
Mehrotra <i>et al.</i> , 2000 <sup>13</sup>	U.S.A.	Retrospective comparative	36	35	11–72	53
Pignatti <i>et al.</i> , 2000 <sup>14,b</sup>	Italy	Retrospective comparative	103	27	1–71	49
Jelinek <i>et al.</i> , 2001 <sup>16</sup>	U.S.A.	Retrospective comparative	54	39	NR	61
Sorensen <i>et al.</i> , 2002 <sup>17</sup>	Denmark	Retrospective comparative	72	31	0.08–77	74
O'Dea <i>et al.</i> , 2003 <sup>18</sup>	Canada	Prospective single-arm	58	41	16–74	60
Abbas <i>et al.</i> , 2004 <sup>19</sup>	U.S.A.	Retrospective comparative	53	39	10–78	55
Duggal <i>et al.</i> , 2004 <sup>20</sup>	Australia	Retrospective comparative	35	32	9–84	46
Sharma <i>et al.</i> , 2006 <sup>21</sup>	South Africa	Retrospective comparative	30	33	10–72	70
Guadagnolo <i>et al.</i> , 2008 <sup>22</sup>	U.S.A.	Retrospective comparative	115	29	8–73	58
Mankin <i>et al.</i> , 2010 <sup>24,c</sup>	U.S.A.	Retrospective comparative	234	37	7–86	61
Rüdiger <i>et al.</i> , 2010 <sup>25</sup>	Australia	Retrospective comparative	34	40	0–81	74
Gluck <i>et al.</i> , 2011 <sup>27</sup>	U.S.A.	Retrospective comparative	95	38	8–87	62
Rutenberg <i>et al.</i> , 2011 <sup>29</sup>	U.S.A.	Retrospective comparative	30	21	8–29 <sup>d</sup>	70
Oudot <i>et al.</i> , 2012 <sup>32,e</sup>	France	Retrospective comparative	44	7	0–15	39
<i>Studies with chemotherapy</i>						
Azzarelli <i>et al.</i> , 2001 <sup>15</sup>	Italy	Phase II single-arm	30	27	4–61	57
Chugh <i>et al.</i> , 2010 <sup>23</sup>	U.S.A.	Phase II single-arm	51	34	12–67	73
Constantinidou <i>et al.</i> , 2011 <sup>26,f</sup>	U.K.	Retrospective comparative	32	27	3–54	79
Penel <i>et al.</i> , 2011 <sup>28</sup>	France	Phase II single-arm study	40	41	20–72	70
Garbay <i>et al.</i> , 2012 <sup>30</sup>	France	Retrospective comparative	62	30	2–66	55
Nishida <i>et al.</i> , 2012 <sup>31</sup>	Japan	Historical prospective	1991–2003: 30	38	7–65	60
		comparative	2003–2011: 22	48	20–86	59

<sup>a</sup> For patients treated in or outside this centre from 1970 to 1992, data were obtained retrospectively from medical records; patients treated from 1993 to 1998 were followed prospectively. Because most were followed retrospectively, we deemed this study to be retrospective.

<sup>b</sup> Of 103 included patients, only 83 were analyzed in the original paper. Age and sex information are provided for 83 patients.

<sup>c</sup> Might include some patients from Spear *et al.*, 1998<sup>10</sup>, but did not conduct a multivariate analysis; the Spear study had a RT-only group and undertook a multivariate analysis.

<sup>d</sup> Patient age data in the original abstract and in the table were discrepant; we report the data from the table.

<sup>e</sup> Of 59 included patients, only 44 had clear comparative data. Age and sex information are provided for 59 patients.

<sup>f</sup> Of 39 included patients, only 32 had clear comparative data. Age and sex information are provided for 39 patients.

RT = radiation therapy; NR = not reported.

TABLE III Outcomes of surgery compared with surgery plus radiation therapy (S+RT) compared with RT alone in desmoid tumours

Reference	Intervention (n patients)	Site <sup>a</sup> (%)	Primary patients (%)	R0 margins (%)		Time (years)	Local control		Toxicity or complications
				Yes	No		Rate (%)	95% CI (%)	
Comparative studies without significant difference for main patient characteristics between groups at baseline or with multivariate analysis									
Goy <i>et al.</i> , 1997 <sup>9b,c,d</sup>	Surgery: 45	Extra-ab: 84 Ab wall: 16	67	47	53	6	Non-R0: 32	8 to 56	Grade 2: 7% Grade 3: 4% Grade 2: 9%
	Surgery + RT: 11 (50–70 Gy)		36	9	91		Non-R0: 78	51 to 100	
Spear <i>et al.</i> , 1998 <sup>10,b,c</sup>	Surgery: 51	Extra-ab: 55 Ab wall: 8 Palmar: 37	71	45	56	5	69		Not available
	RT: 15 (10–72 Gy)	Extra-ab: 73 Ab wall: 20 Palmar: 7	33	—	—		93		Surgery vs. S+RT: 0.03 <sup>e</sup>
Ballo <i>et al.</i> , 1999 <sup>11,b,c,e</sup>	Surgery + RT: 41 (post-op: 10–72 Gy)	Extra-ab: 78 Ab wall: 15 Palmar: 7	37	15	85		72		
	Surgery: 122	Extra-ab: 80 Ab wall: 14 Ab: 6	52	64	36	10	62	53 to 71	Not available
Sorensen <i>et al.</i> , 2002 <sup>17,b,c</sup>	RT: 21 (55 Gy)	Extra-ab: 95 Ab: 5	43	—	—		76	54 to 89	Surgery vs. RT: 0.04 <sup>f,g</sup>
	Surgery + RT: 46 (84% post-op: 60 Gy; 16% pre-op: 50 Gy)	Extra-ab: 98 Ab wall: 2	26	28	72		75	58 to 86	
Sorensen <i>et al.</i> , 2002 <sup>17,b,c</sup>	Surgery: 44	Extra-ab: 69 Ab: 31	100	NA	NA	5	68		Not available
	Surgery + RT (dose NA): 28						82		>0.05

TABLE III Continued

Reference	Intervention (n patients)	Site <sup>a</sup> (%)	Primary patients (%)	R0 margins (%)		Local control			Toxicity or complications
				Yes	No	Time (years)	Rate (%)	95% CI (%)	
Guadagnolo <i>et al.</i> , 2008 <sup>22,b,c,h</sup>	RT: 41	Extra-ab: 96	40	—	—	10	65		Radiation-related complications: mild in 3%, moderate in 10%, severe in 4% (including soft-tissue necrosis, fracture, edema, fibrosis, neuropathy, vascular complications, limb shortening, osteoarthritis, enteritis, radiation proctitis); mesothelioma: 1% after 11 years; carcinosarcoma: 1% after 15 years; melanoma: 1% after 18 years
	(50–75 Gy) Surgery + RT: 74 (44–66 Gy; 9 post-op, 65 pre-op)	Ab wall: 4		30	70		78	>0.05	
Rüdiger <i>et al.</i> , 2010 <sup>25,i</sup>	RT: 17	Extra-ab: 100	59	—	—	4	93		Not available
	(20–60 Gy) Surgery + RT: 17 (20–60 Gy; 13 post-op, 4 pre-op) <sup>j</sup>			88	12	(mean follow-up)	81	>0.05	
Prospective single-arm studies									
O'Dea <i>et al.</i> , 2003 <sup>18,k</sup>	Surgery + RT: 58 (pre-op: 50 Gy)	Extra-ab: 100	57	36	64	≥2	81	NA	Radiation-related complications: fibrosarcoma: 2%; femur and femoral nail fractures: 2%; wound complications: 9% (3% requiring surgical management)
Comparative studies without multivariate analysis to control potential confounders									
Brodsky 1992 <sup>5,b</sup>	Surgery: 28	Extra-ab: 100	66	69	31	NA	68	0.38	Not available
	Surgery + RT (dose NA): 4	Extra-ab: 100				NA	100		

TABLE III Continued

Reference	Intervention (n patients)	Site <sup>a</sup> (%)	Primary patients (%)	R0 margins (%)		Local control			Toxicity or complications
				Yes	No	Time (years)	Rate (%)	95% CI (%)	P Value
Acker <i>et al.</i> , 1993 <sup>6,k</sup>	Surgery: 16 RT: 16 (50–56 Gy)	NA Extra-ab: 88 Ab: 13	100 13	NA	NA	4.5	69 94		NA Not available Left elbow motion decreased: 6%; left leg edema: 6%
Catton <i>et al.</i> , 1995 <sup>7,l</sup>	Surgery: 5 RT: 8 (median: 50 Gy) Surgery + RT: 26 (median: 50 Gy)	Extra-ab: 87 Ab: 13	43	NA	NA	5	80 75 54		NA Not available
Pritchard <i>et al.</i> , 1996 <sup>8</sup>	Surgery: 34 Surgery + RT: 10 (post-op: 90%; pre- and post-op: 10%)	Extra-ab: 100	100	38 20	62 80	5	65 80		NA Not available
Merchant <i>et al.</i> , 1999 <sup>12,b</sup>	Surgery: 74 Surgery + RT: 31 (45–60 Gy)	Extra-ab: 80 Ab wall: 20	100	55	45	4.1	77 77		0.82 Not available
Mehrotra <i>et al.</i> , 2000 <sup>13,m</sup>	Surgery: 17 Surgery + RT: 16	Extra-ab: 100	NA	47 38	53 62	6.9	65 25		NA Not available
Pignatti <i>et al.</i> , 2000 <sup>14</sup>	Surgery: 63 Surgery + RT: 17 (post-op: 50–66 Gy)	Extra-ab: 100	42	100 0	0 100	1.8	55 59		>0.05 Not available
Jelinek <i>et al.</i> , 2001 <sup>16,b,h</sup>	Surgery: 19 Surgery + RT: 35 (post-op: 54 Gy median)	Extra-ab: 100 Extra-ab: 83 Ab: 17	40 30	NR NR	NR	5	53 81		0.02 <sup>e</sup> Not available Radiation-related grade 2 complications: 17% (including recurrent seroma, cellulitis, severe dermatitis, and extremity edema)

TABLE III Continued

Reference	Intervention (n patients)	Site <sup>a</sup> (%)	Primary patients (%)	R0 margins (%)		Local control			Toxicity or complications
				Yes	No	Time (years)	Rate (%)	95% CI (%)	p Value
Abbas <i>et al.</i> , 2004 <sup>19,b</sup>	Surgery: 33 Surgery + RT (dose NA): 19	Extra-ab: 100	42	91	9	4.4	R0: 73 R0: 100		≤0.01 Not available
Duggal <i>et al.</i> , 2004 <sup>20</sup>	Surgery: 27 Surgery + RT: 8 (post-op: 10–64 Gy)	Extra-ab: 100 Extra-ab: 88 Ab wall: 12	71	67	33	5.7	74 75		NA Not available
Sharma <i>et al.</i> , 2006 <sup>21,b,k</sup>	Surgery: 15  Surgery + RT: 15 (post-op: 9–70 Gy)	Extra-ab: 53 Ab wall or intra-ab: 47 Extra-ab: 93 Ab wall or intra-ab: 7	100	NA	NA	>2	At >2 years: 100 86		NA Not available Radiation-related: moist desquamation: 53% of those who received
Mankin <i>et al.</i> , 2010 <sup>24</sup>	Surgery: 177 Surgery + RT (dose NA): 39 Surgery + chemotherapy: 8	Extra-ab: 89 Ab wall or intra-ab: 11	NA	NA	NA	NA	83 87 50		NA Not available
Gluck <i>et al.</i> , 2011 <sup>27,b,k</sup>	Surgery: 54  RT: 13 (50–68.4 Gy)  Surgery + RT: 28 (post-op: 50–68.4 Gy)	Extra-ab: 87 Intra-ab: 13 Extra-ab: 85 Intra-ab: 15 Extra-ab: 96 Intra-ab: 4	93	41	59	3	85 92	70 to 92 57 to 99 43 to 85	0.30 Discontinued RT: 8%; secondary gastric cancer: 8% Chronic pain: 2% Horner's syndrome: 4%; osteonecrosis: 4%; large muscular defect: 4%; nonhealing tissue defect: 7%; limb contracture: 7%; lower limb weakness: 4%; chronic pain: 14%; limitation of motion: 11%; pain combined with limitation: 7%

TABLE III Continued

Reference	Intervention (n patients)	Site <sup>a</sup> (%)	Primary patients (%)	R0 margins (%)		Local control			Toxicity or complications
				Yes	No	Time (years)	Rate (%)	95% CI (%)	p Value
Rutenberg <i>et al.</i> , 2011 <sup>29,b,η</sup>	RT: 15 (40–64.8 Gy)	Extra-ab: 100	33	—	—	5	73		>0.05
	SURGERY + RT: 15 (35–61 Gy; 14 post-op, 1 pre-op)	Extra-ab: 100	47	NA	NA		63–67		Grade 3–4: lymphedema: 7%; spontaneous abortion and pain: 7%; radial or ulnar synostosis: 7%; decreased shoulder ROM: 7% Radiation-related grade 3–4 complications: basal cell carcinoma: 13%; fracture: 20%; cellulitis: 7%; decreased hip ROM: 7%
Oudot <i>et al.</i> , 2012 <sup>32,o</sup>	Surgery: 35	Extra-ab: 90 Ab wall or 10	100	9	91	5	20		NA
	SURGERY + RT: 9 (45–54.4 Gy post-op)	intra-ab:		0	100		44		Not available

<sup>a</sup> “Extra-abdominal” does not include plantar and palmar tumours, Dupuytren disease, Peyronie disease, knuckle pads, or gingival fibromatosis, which are listed separately in the table.

<sup>b</sup> Local failure rate was calculated using the Kaplan–Meier method.

<sup>c</sup> A multivariate analysis was conducted to control potential confounders.

<sup>d</sup> Complications were assessed by study criteria: grade 1, mild symptoms not causing functional disability or requiring reconstructive surgery; Grade 2, requirement for reconstructive surgery or a prosthesis to maintain adequate function; Grade 3, permanent disability or an above-the-knee amputation.

<sup>e</sup> Twelve patients (10 in the surgical group and 1 in each of the other two groups) received doxorubicin-based chemotherapy.

<sup>f</sup> Favoured surgery plus RT.

<sup>g</sup> Favoured RT.

<sup>h</sup> Radiation-related complications were scored as follows: mild (self-limited and requiring no treatment), moderate (requiring conservative medical management), and severe (requiring surgical intervention or hospitalization).

<sup>i</sup> Baseline patient characteristics (including age, sex, lesion size before treatment, and follow-up period) were compared and found not to be significantly different in the intervention groups. Four patients received hormonal therapy (tamoxifen) as an additional treatment.

<sup>j</sup> The surgery plus RT group included 17 patients, but the authors stated that RT was followed by surgery in 13 cases and that surgery was followed by RT in 5 cases. We assumed an error in the case number, with the pre-surgical RT group including 4 patients.

<sup>k</sup> No toxicity criteria were clarified.

<sup>l</sup> Data for 1 patient who received chemotherapy only are not shown in the table.

<sup>m</sup> Data for 1 patient who received surgery plus chemotherapy and for 1 patient who received tamoxifen in addition to surgery plus RT are not shown in the table.

<sup>n</sup> The U.S. National Cancer Institute’s *Common Terminology Criteria for Adverse Events* (version 3.0) were used for toxicity grading.

<sup>o</sup> The study included 59 patients, but only 44 had clear comparative data. Information on desmoid tumour site is based on 59 patients.

CI = confidence interval; ab = abdominal; NA = not available; ROM = range of motion.

## SYSTEMATIC REVIEW OF TREATMENT OPTIONS IN DESMOID TUMOURS

TABLE IV Factors significantly associated with a worse local control rate (LCR) in multivariate analysis

Reference	Used in the multivariate analysis		Significantly associated with a worse LCR	
	Variable	Comparison	Variable	Category
Goy <i>et al.</i> , 1997 <sup>9</sup>	Age (years)	>30 vs. ≤30	—	
	Sex	Men vs. women	—	
	Menses	Yes vs. no	—	
	Trauma	Yes vs. no	—	
	Site	Extremity vs. non-extremity	—	
	Tumour presentation	Primary vs. recurrent	—	
	Tumour size	>10 cm vs. ≤10 cm	—	
	Margin status	Negative vs. positive	Margin status	Positive
	Radiation therapy	Yes vs. no	Radiation therapy	No
Spear <i>et al.</i> , 1998 <sup>10</sup>	Age (years)	≥18 vs. <18	Age (years)	<18
	Sex	Men vs. women	—	
	Tumour presentation	Primary vs. recurrent	Tumour presentation	Recurrent
	Plantar site	Yes vs. no	—	
	Margin status	Negative vs. positive	Margin status	Positive
	Radiation therapy	Yes vs. no	Radiation therapy	No
Ballo <i>et al.</i> , 1999 <sup>11</sup>	Age (years)	>30 vs. ≤30	Age (years)	≤30
	Sex	Men vs. women	—	
	Tumour location	Head vs. trunk vs. extremity	—	
	Tumour presentation	Primary vs. recurrent	—	
	Prior treatments ( <i>n</i> )	>1 vs. ≤1	—	
	Tumour size	>5 cm vs. ≤5 cm	—	
	Treatment type	Surgery vs. RT vs. surgery plus RT	Treatment type	Surgery
	Adjuvant chemotherapy	Yes vs. no	—	
Sorensen <i>et al.</i> , 2002 <sup>17</sup>	Age (years)	≥31 vs. <31	Age (years)	<31
	Sex	Men vs. women	—	
	Tumour size	>4 cm vs. ≤4 cm	Tumour size	> 4 cm
	Tumour location	Extra-abdominal vs. abdominal	Surgical classification	Extra-abdominal
	Surgical classification	Extra- vs. intracompartmental	—	
	Margin status	Negative vs. positive	Margin status	Positive
	Radiation therapy	Yes vs. no	—	
Guadagnolo <i>et al.</i> , 2008 <sup>22</sup>	Age (years)	>30 vs. ≤30	Age (years)	≤30
	Sex	Men vs. women	—	
	Tumour location	Head and neck vs. trunk vs. upper extremity vs. lower extremity	—	
	Tumour presentation	Primary vs. recurrent	—	
	Tumour size	<5 cm vs. 5–10 cm vs. >10 cm	Tumour size	5–10 cm and >10 cm
	Treatment type	RT vs. surgery plus RT	—	
	RT dose	≤56 Gy vs. >56 Gy	—	
	RT portal margin	<5 cm vs. 5–7 cm vs. >7 cm	—	

RT = radiation therapy.

TABLE V Outcomes in chemotherapy studies of desmoid tumours

Reference	Intervention	Pts (n)	Site <sup>a</sup> (%)	Primary patients (%)	PFS (%)	Response rate (%)			Grades 3–4 toxicity
						Complete response	Partial response	Stable disease	
Phase II trials									
Azzarelli <i>et al.</i> , 2001 <sup>15,b,c</sup>									
	Methotrexate 30 mg/m <sup>2</sup> plus vinblastine 6 mg/m <sup>2</sup> , every 7–10 days, by intravenous bolus infusion to a median of 38 cycles	30	Extra-ab: Intra-ab: 10	20	5-Year: 67 10-Year: 67	0	Median 1-year: 40	60	0 0 Leukopenia, 93%
Chugh <i>et al.</i> , 2010 <sup>23,b,d,e</sup>									
	Twice-daily oral imatinib 300 mg for BSA ≥ 1.5 m <sup>2</sup> , 200 mg for BSA 1.0 m <sup>2</sup> to <1.5 m <sup>2</sup> 100 mg for BSA < 1.5 m <sup>2</sup>	51	Extra-ab: Intra-ab: 16	≤22	2-Month: 94 4-Month: 88 1-Year: 66 3-Year: 58	0	0	4-Month: 84	10 6 Neutropenia, 10%; rash, 10%; fatigue, 8%
Penel <i>et al.</i> , 2011 <sup>28,b,e,f,g</sup>									
	Imatinib 400 mg daily to 12 months or 400 mg twice daily to 6 months	35	Extra-ab: Ab wall: Intra-ab: 20	<15	2-Year: 55 (95% CI: 39 to 69)	3	9	80	9 0 Rash, 10%; abdominal pain, 10%; vomiting or nausea, 13%; diarrhea, 5%; myalgia, 5%; asthenia, 5%; secondary cancer (clear cell renal carcinoma), 2.5%
Studies that did not compare patient characteristics between groups at baseline									
Constantinidou <i>et al.</i> , 2011 <sup>26,e,g</sup>									
	Methotrexate 50 mg and vinblastine 10 mg for 3 weeks to 12 months	18	Extra-ab: Ab wall: Intra-ab: 28	6	NA	0	11	60	22 6 Mucositis, 22%; peripheral neuropathy, 17%; vomiting, 17%; neutropenia, 17%
	Peg-dox 40–50 mg/m <sup>2</sup> every 4 weeks for up to 6 cycles	14	Extra-ab: Intra-ab: 21	0		0	29	57	0 14 Grade 2 or 3 palmar– plantar erythema, 36%; grade 2 or 3 mucositis, 29%

TABLE V Continued

Reference	Intervention	Pts (n)	Site <sup>a</sup> (%)	Primary patients (%)	PFS (%)	Response rate (%)			Grades 3–4 toxicity
						Complete response	Partial response	Stable disease	
Garbay <i>et al.</i> , 2012 <sup>30,e,g</sup> Anthracycline-containing <sup>h</sup>	Non-anthracycline-containing <sup>i</sup>	13	Extra-ab: 100	<50	NA	0	54	46	0 0 Massive necrosis, secondary peritonitis, and death, 8%; at least 1 hematologic adverse event, 31%
		49	Extra-ab: 100			2	10	63	24 0 At least one hematologic adverse event, 10% ( $p=0.06$ )
Nishida <i>et al.</i> , 2012 <sup>31,g,j</sup>	Surgery (1 patient received post-op RT)	30	Extra-ab: >70 Ab wall: <30	80	LCR: 47	NA			Not available
	Meloxicam 10 mg daily	22	Extra-ab: 86 Ab wall: 14	100	NA	5	45	36	5 9

<sup>a</sup> “Extra-abdominal” does not include plantar or palmar tumours, Dupuytren disease, Peyronie disease, knuckle pads, or gingival fibromatosis, which, if present, are separately listed in the table.

<sup>b</sup> Progression-free survival was calculated using the Kaplan–Meier method.

<sup>c</sup> Tumour response was assessed by World Health Organization criteria. Toxicities were graded using the comprehensive criteria set out by Ajani *et al.*, 1990<sup>52</sup>.

<sup>d</sup> Tumour response was assessed by study-defined criteria: complete response, disappearance of evidence disease; partial response, >30% shrinkage of uni-dimensional measurable disease and no evidence of progressing or new lesions; progressive disease, an increase of at least 30% or 3 cm in measurable disease, appearance of new lesions, reappearance of a prior lesion, or a significant deterioration in symptoms; stable disease, neither sufficient shrinkage to qualify for partial response, nor sufficient increase to qualify for progressive disease.

<sup>e</sup> The U.S. National Cancer Institute’s *Common Terminology Criteria for Adverse Events* (version 3.0) were used for toxicity grading.

<sup>f</sup> The study recruited 40 patients with 44 lesions, with 35 patients being analyzed at 3 and 6 months, and 21 being analyzed at 12 months.

<sup>g</sup> Tumour response was assessed using the Response Evaluation Criteria in Solid Tumors. Definitions: complete response, disappearance of all measurable and non-measurable lesions; partial response, at least 30% decrease in the sum of the longest diameter of measurable lesions (taking as a reference the baseline sum of the longest diameters of the measurable lesions); progressive disease, at least a 20% increase in the sum of the longest diameter of target lesions (taking as a reference the smallest sum of the longest diameters recorded since treatment started) or the appearance of new lesions; stable disease, neither sufficient shrinkage to qualify for a partial response nor a sufficient increase to qualify for progressive disease.

<sup>h</sup> Regimens: doxorubicin 20 mg/m<sup>2</sup>, ifosfamide 2.5 g/m<sup>2</sup>, and dacarbazine 300 mg/m<sup>2</sup>, days 1–3; doxorubicin 20 mg/m<sup>2</sup> and dacarbazine 300 mg/m<sup>2</sup>, days 1–3; doxorubicin alone 60–75 mg/m<sup>2</sup>, 21-day cycle.

<sup>i</sup> Regimens: methotrexate 30 mg/m<sup>2</sup> and vinblastine 6 mg/m<sup>2</sup>; methotrexate alone 30 mg/m<sup>2</sup>, 28-day cycle; metronomic oral etoposide 75 mg daily, 21- or 28-day cycles; vinblastine 20 mg/m<sup>2</sup>, 21-day cycles.

<sup>j</sup> Data for the surgery group were extracted from Shido *et al.*, 2009<sup>53</sup>, which did not meet the preplanned section criteria for the present study.

Pts = patients; PFS = progression-free survival; PD = progressive disease; ND = not determined; ab = abdominal; BSA = body surface area; CI = confidence interval; NA = not available; Peg-dox = pegylated liposomal doxorubicin; LCR = local control rate.

#### 4. DISCUSSION

In answering an interventional research question, RCTs provide the highest level of evidence. When RCTs are unavailable or are methodologically flawed, well-designed prospective comparative studies can provide supplemental evidence that might address the research question. All twenty-eight studies that are summarized and interpreted in the present systematic review are non-RCTs. Overall, the quality of the included studies was poor to moderate. Thus, the quality of the evidence from the included studies is also low to moderate, which is common for rare diseases. Considering only the studies that attempted to control for potential confounders, the evidence generally supports the conclusion that, compared with surgery alone, surgery plus RT is associated with a higher local control rate. No statistical difference in local control was observed for RT alone compared with surgery plus RT in patients with primary or recurrent desmoid tumours.

Meta-analyses of these trials were deemed not feasible because of heterogeneity in patient characteristics, tumour sizes, tumour presentation (primary or recurrent), tumour locations, margin status, type of interventions, intervention doses, and so on. Because the original intervention treated a benign condition, often in a young person (mean or median age: 7–41 years in the eligible studies), some radiation-related complications—namely, secondary malignancy—should be considered when making treatment recommendations. Although the radiation dosages used in the studies covered a wide range (9–75 Gy), complication rates increased significantly with doses exceeding 56 Gy<sup>11</sup>. Comparing surgical morbidity between retrospective studies in a meaningful way to help in making treatment decisions is very difficult.

Of the five studies that conducted a multivariate analysis (Table IV), not all controlled for the same confounders. Potential confounders might have been missed in the multivariate models in some studies. Three studies included margin status as a variable in the models, and all the studies showed that positive margin status led to a worse local control rate. All five studies included age in their models, and four of the studies indicated that younger age (30 years of age or younger in three studies, and 18 years of age and younger in one study) was predictive of a worse local control rate (two studies compared surgery with RT and with surgery plus RT<sup>10,11</sup>, one study compared surgery with surgery plus RT<sup>17</sup>, and one study compared RT with surgery plus RT<sup>22</sup>). Age was determined to be an independent risk factor for recurrence whether the patients were treated with RT or not. If possible, negative margin status (defined as a surgical resection with microscopically negative margins) should therefore be achieved for a patient who needs surgical treatment and a young patient who might be at a higher risk for local relapse.

The current evidence for systemic therapy in the target population that meets our criteria for inclusion is limited. Many studies conducted for patients with desmoid tumours recruited fewer than 30 patients and were therefore excluded. Although many smaller studies are used by clinicians in treatment decision-making, a sample size of 30 is, from a statistics perspective, the minimum acceptable number to support the assumption of normal distribution for reporting outcomes with 95% confidence intervals<sup>54</sup>. Three single-arm phase II studies demonstrated that imatinib alone or methotrexate plus vinblastine were effective, but were associated with grade 3 or 4 toxicities<sup>15,23,28</sup>. Imatinib is a selective receptor tyrosine kinase inhibitor. The 2006 Heinrich *et al.*<sup>55</sup> study, with 19 patients, reported that imatinib response in patients with desmoid tumours might be mediated by inhibition of *PDGFRB* kinase activity. However, in the 2010 Chugh *et al.*<sup>23</sup> study, expression and polymorphisms of target proteins were identified in tissue samples from 20 of 51 patients, and no significant correlation of target proteins with outcome was observed.

#### 5. CONCLUSIONS

Desmoid tumours are rare, and the heterogeneity in their treatment is reflected in the poor quality of the available literature. Our attempt at a systematic review of the literature did not yield very satisfying information, except that, compared with surgery alone, surgery plus RT likely results in a higher local control rate. Although clinicians must consider the long-term consequences of RT in young patients with benign tumours, it is difficult to directly compare those effects against the long-term morbidity of large surgical resections. The available data do not directly compare the efficacy of systemic treatment with that of surgery or RT (alone or combined), and therefore specific recommendations cannot be made. Given the increasing trend toward the use of systemic therapies, data are likely to emerge about the various systemic options. To date, surgery, RT, and systemic therapy alone have all been effective for patients with desmoid tumours. Given that desmoid tumours are non-malignant and non-metastasizing, and given the unclear risk–benefit ratios of the various treatment options, patients should be informed of all risks and benefits during treatment decision-making, and patient preferences should be taken into consideration.

The evidence from the existing literature is unable to answer the following clinically important questions:

- When should RT be used alone or in combination with surgery, and what should the dose be?
- What is the role of surgery alone in the treatment of desmoid tumours?
- Is there a patient population that is at higher risk of relapse in the absence of adjuvant RT?

- Should adjuvant RT be given to patients with positive margins, or should those patients undergo another surgery?
- Is positive margin status a marker of inherently more aggressive disease or of a difficult disease location?
- Is there a role for systemic treatment in neoadjuvant cytoreduction to obtain negative margins?
- What should be the sequence of use for the various modalities?

Thus, well-designed, well-powered, and high-quality RCTs or prospective comparative studies are expected and required to adequately address these research questions.

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## 7. CONFLICT OF INTEREST DISCLOSURES

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